M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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To: Dockets Management Branch (HFA-305)

From: Melissa Lamb
Office of Generic Drugs

Subject: BE Recommendations for Locally Acting Nasal and Pulmonary Drug Delivery

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation: Conference VI Nasal and Pulmonary Drug Delivery

Presented for: Be Recommendations for Locally Acting Nasal and Pulmonary Drug Delivery

Date Presented: 9/28/1999

Presented by: Wally P. Adams, Ph.D.

Number of Pages: 21

Melissa Lamb

Attachment

90S-0308

M673

BE Recommendations for Locally Acting Nasal Aerosols and Nasal Sprays - An FDA Viewpoint

Conference VI

Nasal and Pulmonary Drug Delivery

Rome, Italy
28 September 1999

Wallace P. Adams, Ph.D.
Office of Pharmaceutical Science
CDER/FDA

These slides represent the personal opinions of the speaker and do not necessarily represent the views or policies of US FDA.

Draft Guidance Coverage

- Bioavailability (BA) Measurement
  - May be noncomparative
  - Characterization (benchmark) studies
  - PRODUCT QUALITY BA ONLY
  - Additional PK/Bio studies are not covered
- Bioequivalence (BE) Establishment
  - Comparative studies
- Covers locally acting drug products only

Locally Acting Drug Products (LADP)

The BE Challenge:

Delivery to sites of action does not occur primarily after systemic absorption, hence

Pharmacokinetic studies are inadequate to fully document BE

Approaches to Establish BE

- Pharmacokinetic
- Pharmacodynamic
- Clinical
- In vitro

BE Concepts for LADP

- Local delivery
  - relates to efficacy
- Systemic exposure
  - relates to safety
  - may also relate to efficacy
    - e.g., levocabastine nasal spray

General BE Approach

- Formulation equivalence:
  - Q1 (excipients qualitatively the same)
  - Q2 (excipients quantitatively the same)
- Functional comparability of devices
- Solutions
  - In vitro BE
- Suspensions
  - In vitro BE
  - In vivo studies (two)

Pharmaceutical Inequivalence

- A test product with different inactive ingredient(s), or different valve, pump, or actuator (container and closure system), which requires redocumentation of safety and/or efficacy.

In Vitro BE Data

- Apply to all aerosols and sprays
- Considered to be more sensitive indicators of differences in drug delivery to nasal sites than are clinical data
- Confidence intervals for comparative data of selected in vitro BE measures
- Statistics under development for the selected in vitro BE measures

In Vitro BE Data: Specific Tests

- Dose or spray content uniformity through container life
- Droplet size distribution
- Drug particle size distribution
- Spray pattern and plume geometry
- Priming and repriming
- Tail off

In Vitro Population BE Criterion and BE Limit

$$\frac{(\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2)}{\sigma_R^2} \leq \theta$$

μ_T, μ_R = T and R means (log scale)

σ_{BT}, σ_{BR} = between batch T and R standard deviations (log scale)

σ_{CT}, σ_{CR} = between canister T and R standard deviations (log scale)

$\sigma_R^2 = \sigma_{BR}^2 + \sigma_{CR}^2 + \sigma_{LR}^2$

$\sigma_T^2 = \sigma_{BT}^2 + \sigma_{CT}^2 + \sigma_{LT}^2$

σ_{LT}, σ_{LR} = within T and R canister between life stage standard deviation

θ = in vitro BE (upper) limit

In Vivo BE Data

- LOCAL DELIVERY based on clinical study
- SYSTEMIC EXPOSURE based on PK study, or
- SYSTEMIC ABSORPTION based on PD or clinical study
- In vivo data requested for suspension formulations only

Clinical Study for Local Delivery

- BE (NDA):
  - may use the same comparative studies used to establish S and E of the drug product
- BE (ANDA):
  - Three suggested clinical BE study designs
- Sensitivity based on dose-response

Systemic Exposure or Systemic Absorption:

Which is Preferred?

- Preferred study:
  - PK study in healthy subjects
- Alternative when PK not feasible:
  - PD or clinical study in healthy subjects

Emphasis on In Vitro Data for Establishing BE

- Clinical studies are highly variable and relatively insensitive to product differences
- *Therefore*
- BE studies with PD or clinical endpoints will not be sufficient in the event of in vitro BE studies that fail to meet the criteria

Number and Type of Batches (Draft Recommendation)

- BE (in vitro studies):
  - 30 (min) for TEST; 10 cans or bottles from each of three batches
    - three different primary stability batches
  - 30 (min) for REFERENCE; 10 cans or bottles from each of three batches
    - three different batches from the marketplace

Batches for Clinical BE Study for Local Delivery (Draft Recommendation)

- NDA
  - Same batches used for in vitro BE studies
- ANDA
  - Test and RLD batches used in the in vitro BE studies

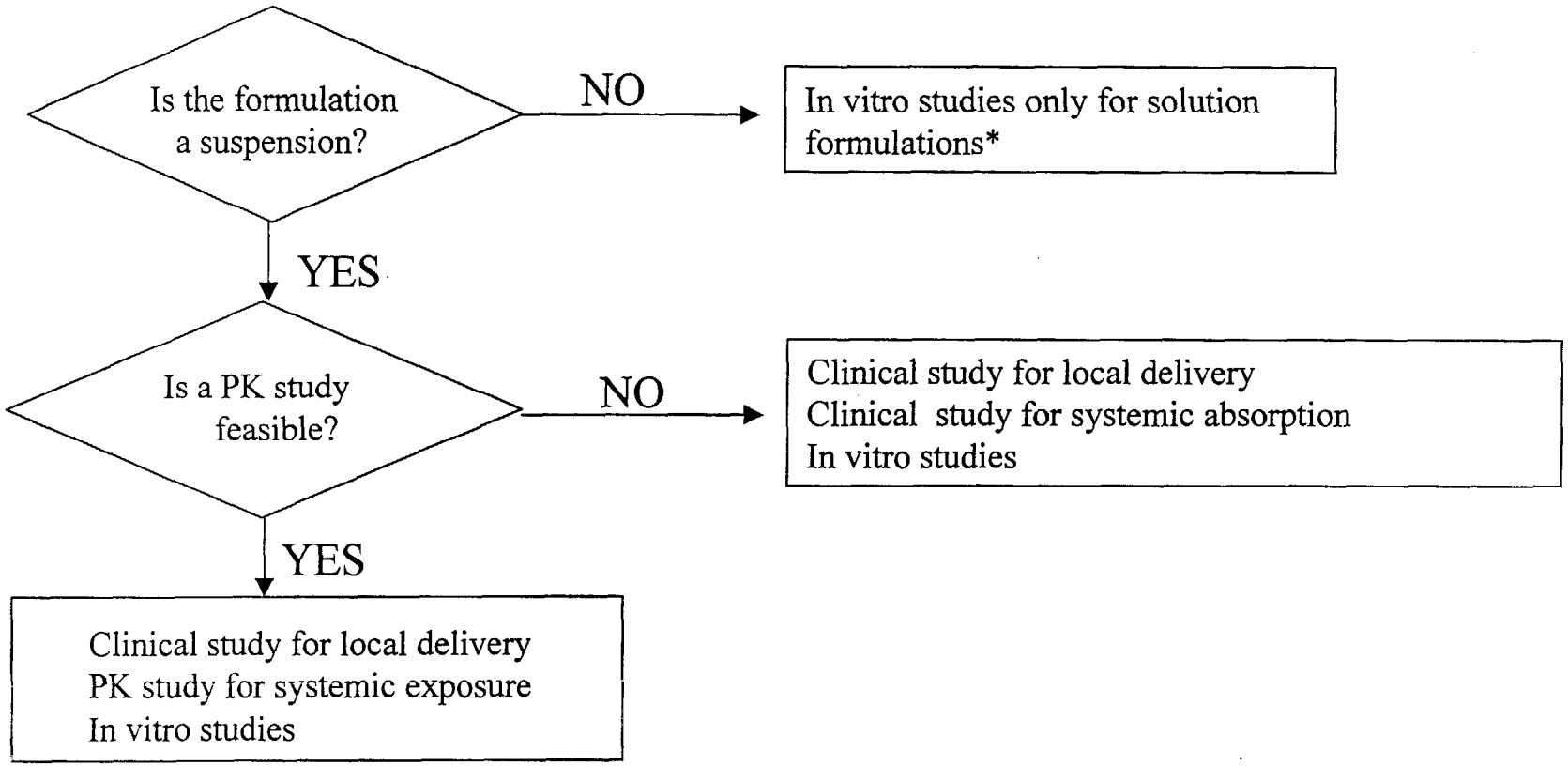
Batches for Systemic Exposure or Systemic Absorption BE Study (Draft Recommendation)

- NDA
  - Batches used in the in vitro testing
- ANDA
  - Test and RLD batches used in the clinical study for local delivery, with in vitro BE data

Draft Nasal BA/BE Guidance: Continuing Work Includes -

- Multiple batch data: statistical approaches
- Establishing BE limits for comparative in vitro data
- Interest in reduction in in vitro testing for certain measures
  - Objective vs subjective evaluation
  - Three batch data for statistical evaluation
  - Consideration of one batch test and RLD data for supportive characterization without statistical consideration
- Response to public comments sent to docket

Decision Tree For Product Quality
BA and BE Studies For Nasal Aerosols and Nasal Sprays



*See Section II (A) regarding additional in vivo BA studies needed for solution and suspension formulations.

Acknowledgments

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- Office of Generic Drugs
- Office of Clinical Pharmacology and Biopharmaceutics
- Division of Pulmonary Drug Products
- Division of Testing and Applied Analytical Development
- Division of Product Quality Research
- Quantitative Methods and Research Staff
- Thomas Jefferson University/Biostatistics Section

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Table 1
In Vitro BA and BE Studies for Nasal Aerosols and Nasal Sprays

TEST	BA AND BE STUDY MEASURE(S)[1]	BE MEASURES[2]	LIFESTAGE(S) B (beginning) M (middle) E (end)	CONFIDENCE INTERVAL OR SUPPORTIVE CHARACTERIZATION FOR BE	GUIDANCE SECTIONS
Dose or spray content uniformity through container life	Drug mass per single dose	Same as previous column	B, M, E (aerosols) B, E (sprays)	Confidence interval	V.B.1, IX.B
Droplet size distribution	D_{10}, D_{50}, D_{90}, span	D_{50}, span	B, M, E	Confidence intervals	V.B.2, IX.B
Particle size distribution (CI or MSLI)	Deposition profile over 3 groups	Same as previous column	B, E	Confidence interval	V.B.2, IX.D
Drug and aggregate PSD of suspensions (light microscopy)	Drug CMD and GSD; aggregate PSD	Drug CMD	B	Supportive characterization	V.B.2, IX.C
Spray pattern	D_{max}, D_{min}, ovality ratio	D_{max} or D_{min}, ovality ratio	B, E	Confidence intervals	V.B.3, IX.B
Plume geometry	Length, width, spray cone angle (if feasible)	Same as previous column	B	Supportive characterization	VB.4, IX.C
Priming and repriming	Drug mass per single actuation	Same as previous column for: • priming, and • repriming if in precursor product (R) labeling	From first actuation (priming); from first actuation after specified period of nonuse (repriming)	Confidence interval for priming and repriming if in precursor product (R) labeling; supportive characterization of priming when not in labeling	V.B.5, IX.B, IX.C
Tail off	Drug mass per single actuation	Same as previous column	From end of labeled number of actuations to exhaustion	Supportive characterization	V.B.6, IX.C

[1] Data requested as part of the BA or BE submission.
[2] Measures requested for comparative in vitro BE documentation.